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Does Exercise Reduce Depressive Symptoms? Commentary Review on Efficacy, Mechanisms and Implementation

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ABSTRACT

This commentary review collates and evaluates current review and meta-analysis evidence on the association between exercise and depression. Collectively this evidence demonstrates a clear and robust effect of depressive symptom reduction as a result of exercise, and this effect is shown to be particularly stronger in populations with greater severity of depressive symptoms. Examination of potential mechanisms to explain this effect reveals factors at biological (e.g. neuroendocrine, neurotrophic, oxidative, and cortical pathways), psychological (e.g. self-efficacy, mastery, cognitive distraction), and social levels (e.g. reduced social isolation, social support). Furthermore, there appear to be several additional indirect effects (e.g. improved physical wellbeing, reductions in comorbidity) that further contribute to reduced depression. Taken together the evidence shows exercise can reduce depressive symptoms, and plausible mechanisms exist to explain this effect. However, whilst efficacy is demonstrated, this commentary review also highlights potential issues for implementation within clinical practice. The evidence suggests that whilst exercise may be a viable treatment option compared to no treatment, there is yet no evidence of superiority in comparison to traditional treatment pathways. This raises questions on implementation due to the notable association of treatment drop-out and non-adherence within populations with depression. To address this issue a number of relevant strategies are discussed in relation to interventions that use exercise.

EXERCISE AND HEALTH

Physical activity and exercise (exercise, i.e. planned, structured physical activity to improve physical health; [1]) have benefits on a person's health. It is well accepted, via robust research spanning many decades, that being physically active is associated with positive effects in a range of bodily systems including circulatory, respiratory, endocrine, musculoskeletal, digestive, nervous, immune and lymphatic system [2,3]. Importantly being physically active and participating in exercise has been shown to be protective against many major diseases associated with these bodily systems (e.g. stroke, chronic obstructive pulmonary disease, musculoskeletal pain, type 2 diabetes, cancers), and can also facilitate recovery (or halt progression) in many of these diseases [3,4]. There is global recognition of these health benefits; the Lancet Physical Activity Series stated that insufficient physical activity is a leading cause of premature mortality, with the World Health Organisation planning global action to tackle this problem [5,6].

EXERCISE AND DEPRESSION

Evidence also suggests that physical exercise can confer benefits beyond biological systems and has positive effects on mental health [4]. Depression has featured as a particular area of research focus in this regard [7,8]. Depression is conceptualized by the presence of symptoms related to low mood and negative self-appraisal, low levels of energy and fatigue, sleep disturbance, appetite changes, behavioural changes (apathy, agitation), and thoughts of/or actual self-harm [9]. A core feature of depression (as opposed to feeling "down" from time to time) is symptom persistence, and in terms of clinical depression (e.g. Major Depressive Disorder, MDD) there is a significant impact on a person's ability to function at work and at home, and some form of intervention is required [9,10]. Depressive symptoms are common in society, with population prevalence estimates between 10% to 15%, with MDD population prevalence estimates at 4% to 8% [11,12]. Treatments most often involve pharmacological (e.g. anti-depressant medication) and/or psychological (e.g. Cognitive Behavioural Therapy; CBT) approaches [13]. Evaluation of current treatments suggest only moderate efficacy, and the search is on for alternative treatment options to reduce adverse events (mainly pharmacological dependency) and improve treatment adherence [13,14].

In line with the search for alternative treatments for depression is an accumulating body of evidence assessing whether exercise is a suitable option. Early research in this area observed that neurobiological changes as a result of exercise were active within the regions and systems associated with depression, notably affecting neuroendocrine, neurotrophic, inflammatory, oxidative regulation and cortical brain areas [7]. A number of clinical trials and studies have since been conducted to test whether exercise can reduce depressive symptoms, with collective evidence presented in a number of systematic review and meta-analysis publications. A Cochrane review [15] of 28 trials (25 included within their meta-analysis) reported an overall large effect size (standardized mean difference, SMD 0.82) favoring exercise compared with control arms, though this effect size was significantly lessened (SMD 0.62) when the authors applied more stringent criteria (e.g. only including studies that employed blinding). In addition, no differences were reported when comparing exercise to other treatment arms (i.e. not superior to anti-depressants or CBT). However, the authors of this Cochrane review did note significant population heterogeneity within their included studies; in particular an issue of case mix (populations including both those with mild and more severe forms of depression), highlighting a need for further research to assess potential subgroup differences. A later meta meta-analysis [16], considering the effects of physical activity in non-clinical populations of those with depression or anxiety, reported on two meta-analyses specifically on depression (92 studies, n = 4310). Results of this meta meta-analysis show an overall medium effect size (SMD 0.50), again supporting the hypothesis that exercise can reduce depressive symptoms. A further meta-analysis [8] aimed to overcome some of the earlier bias issues reported by earlier meta-analyses (e.g. Cochrane review by Mead et al. [15]). This new review by Schuch[b] et al. [8] reported an overall sizable large effect size (SMD 1.11) when controlling for biases and heterogeneity. In further subgroup analysis that separated depressive sub-populations (non-clinical, clinical), they reported a larger effect size of exercise on symptom reduction in those with MDD (SMD 1.14). Interestingly, this effect was increased in those with a greater severity of symptoms, in those who were older in age, and in those with increased comorbidity. Overall the meta-analysis by Schuch[b] et al. [8] report a sizable and clinically meaningful reduction in depressive symptoms as a result of exercise; equivalent to -5 points on the Hamilton Rating Scale for Depression ([17], or -6 points on the Beck Depression Inventory [18].

Taken collectively the evidence from these meta-analyses clearly demonstrate the benefit of exercise on the reduction of depressive symptoms, and this effect appears stronger (and clinically useful; [19]) in those with clinical level depression, with further additional effect in those with comorbidity (thought to be attributed to the effect of exercise on other health conditions leading to indirect influences). This accumulating evidence has initiated the promotion of psychical health and exercise within depression treatment guidelines, for example National Institute of Clinical Excellence (NICE) guidelines in the UK [20], and recent guidance for the European Psychiatric Association [21].

Does Exercise Reduce Depressive Symptoms? Commentary Review on Efficacy, Mechanisms and Implementation. Anxiety And Depression Journal. 2020; 3(1):121.

MECHANISMS OF EFFECT

The mechanisms of the effect of exercise on depression are complex and include potential bio-psychosocial pathways [3]. The following section will outline the evidence of potential mechanisms of effect for these pathways.

Biological pathways

A recent systematic review of studies on those with MDD [7] examined evidence of biomarker responses to exercise across five current biological hypotheses (neuroendocrine, neurotrophic, inflammatory, oxidative and cortical volume).A brief outline of these findings will be presented here, a more in-depth discussion of these results can be found within the original review [7]. On neuroendocrine effects, the authors examined two studies that had measured cortisol presence (a marker of elevated stress levels brought about by activation of the hypothalamic-pituitary-adrenocortical axis, which is the body's central stress response system; [22]) and report no evidence of change. However, they did find evidence in one study of another marker of elevated stress (copeptin; [23]), which was shown to increase in the acute phase (i.e. just after exercise) but then decrease in the long term (in the weeks following exercise). The review also reported on two studies that considered changes in prolactin (proxy indicator of serotonergic secretion, a process known to be robustly associated with depression and involved in the synthesis of anti-depressive medication; [24]) which found no change as a result of exercise, but did report on two studies that found increases in growth hormone. Such increase in growth hormones are thought to stimulate neurogenesis, understood to be important in increasing overall neuroplasticity, and may play an important role in the optimal synthesis of anti-depressant medication [25]. For neurotrophic effect, the authors report on two studies that had found increases in Nerve Growth Factors (NGF), and NGF has been shown to be associated with increased neuronal plasticity, again thought to be an important moderator of anti-depressant efficacy [26]. The review also reported on evidence of Brain Derived Neurotrophic Factor (BDNF), which has been shown to be depleted in those with depression, but elevated after exercise in animal models [27]. Results from the review show no evidence of significant change in BDNF from serum sampling, however the authors do comment that these particular studies were confounded by patient heterogeneity, and presence of anti-depressant pharmacology which can disrupt BDNF levels. For inflammatory markers (thought to mediate the harmful effects of depression; [28]), the authors report no significant change in pro-inflammatory cytokine levels as a result of exercise. Evidence of oxidative change (oxidative stress shown to be associated with depression, more so in those with long term depression; [29]) was found in one study within the acute phase and it is thought that stimulation of oxidative stress from exercise would stimulate greater levels of neuronal repair. Finally, the review reports on cortical volume within the hippocampus (shown to be reduced in those with MDD; [30]), the authors report on a single study that found increased hippocampal cortical volume over time. Overall the evidence demonstrates that biological pathways may give some explanation to the beneficial effects of exercise on depression, in particular neuroendocrine, neurotrophic, oxidative and cortical pathways. However, many of the individual findings outlined within the Schuch[a] et al. [7] review are based on a small number of studies, and more evidence is required before robust conclusions can be drawn.

Psychological and social pathways

A recent meta review [21] and editorial commentary [31] both commented that the effects of exercise on those with depression are likely to be multidimensional, with important mediators (explaining the effect) and moderators (changing the effect) at a psychosocial level. Examining evidence of psychosocial effects as reported within the meta-analysis papers described above [7,8,15,16] and this more recent review and commentary ([21,31] respectively), show consensus on the effects of exercise across a number of psychological and social factors. One key recurrent theme that emerges from this evidence is the concepts of mastery and self-efficacy (feelings of confidence in activities and duties, and feelings of self-worth, both shown to be greatly reduced in those with depression; [12,32]). These constructs were shown to significantly increase as a result of participation in exercise, thought to give the patient a sense of mastery over a new skill and increase self-confidence. Evidence also shows that exercise was associated with a reduction in fatigue levels and improved sleep hygiene, both of which are a core feature of depressive symptoms [33,34]. Another beneficial psychological feature thought to play an important role was "cognitive distraction",

the actual act of exercise reduced time for participants to focus on negative thoughts (negative attentional and interpretational biases are common in depression; [35]) and supplanted positive thoughts associated with achievement and mastery. Furthermore, the evidence showed greater effects of exercise on participants who had received ongoing supervision and support [8], and this may be as a result of the benefits of positive reinforcement from supervising staff (e.g. behavioural activation/reinforcement influences; [36]). There is also evidence of social factor influences. Evidence showed reductions in reported social isolation levels (a key feature of depression; [37]). Increases in social support (from other participants as well as instructors and clinical staff) were also reported; increases in social support has been shown to associate with reduction in depressive symptoms [38,39], in addition social participation has been shown to influence positive social cognitive processes (attributions of others, interpretation of others) in those with depression [40].

The evidence directly above suggests that exercise can influence depressive symptoms via a number psychological and social pathways. In addition to these direct effects are wider influences as reported in the conclusions of two aforementioned reviews [8,21]. These reviews comment on residual effects of exercise at a biopsychosocial level, based on the findings that clinical improvement was greatest in those with more severe depressive symptoms and those who reported greater levels of comorbidity. Explanations for this effect are improved overall lifestyle factors (better diet, reductions in smoking, additive effects of exercise on cardiovascular, respiratory and metabolic conditions) leading to increases in general quality of life and wellbeing. Overall the evidence suggests a cascade effect of exercise that directly influences via multiple biopsychosocial pathways directly related to depression, as well as evidence of broader indirect influences.

IMPLEMENTATION

Whilst the evidence above clearly shows the benefit of physical exercise on the reduction of symptoms in those with clinical depression, and demonstrates viable pathways to explain this effect, there remain some important considerations. Many of the reviews and meta-analyses (as outlined above) comment on specific issues such as high dropout rates and attrition within various intervention trials. Treatment adherence is one of the key challenges for the management of depression, with patients with depression being more than twice as likely to be non-adherent [41]. For example, Stubbs et al [21], in their meta review and guideline statement, show the dropout rates of 31 exercise based randomized controlled trials for those with MDD was between 13% to 21%. This raises particular issues for what is arguably a more intrusive intervention (e.g. requires personal investment of time and sustained effort) compared to standardized pharmacological treatments. A recent project that developed a tool kit for exercise interventions designed for those with depression has recognized these particular issues of non-adherence [42]. They recommend consideration of the following for successful implementation; literature for patients and clinicians to explain the benefits of exercise, training for clinicians on assessment to consider appropriate dosage (e.g. due to comorbidity, fatigue, depressive severity), addressing low motivation levels in patients by providing emotional support and guidance (e.g. motivational interviews), continued supervised support during exercise, involvement in group activity (increase general social support), and the setting of goals with regular ongoing progress review.

CONCLUSION

It is clear that physical exercise can benefit those who have clinical depression. The mechanisms to explain this effect are complex and operate at a biopsychosocial level. These mechanisms involve factors that directly influence depressive symptoms, as well as indirect factors that can have wider beneficial effects on general health and lifestyle. The key challenge at present is not whether exercise is beneficial, the evidence is strong that it is, but more so on how exercise can be successfully implemented in a clinical population that is associated with low motivation, treatment resistance/nonadherence, and relapse. Future pragmatic implementation research is now required to investigate these issues further in order to increase confidence in considering exercise as part of the clinical tool kit.

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